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Leishmaniasis: a vector- born disease in Sri Lanka: past, current and future

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Abstract

Leishmaniasis is caused by a protozoan parasite *Leishmania* species and is transmitted to humans by the bite of infected female phlebotomine (Diptera: Psychodidae) sand flies. There are three main forms of Leishmaniasis; Cutaneous Leishmaniasis, Muco-Cutaneous Leishmaniasis and Visceral Leishmaniasis. At present, Cutaneous Leishmaniasis is established in Sri Lanka. The parasite in this country is *Leishmania donovani* MON 37 and the prevalent vector is *Phlebotomus argentipes*. Environmental factors including temperature, humidity and rainfall influence the abundance and distribution of sand flies. Socio-economic conditions, population mobility, environmental and climate changes are the main risk factors of the spread of Leishmaniasis. Early detection of the disease and treatment, vector management and health education are the main control strategies for the control of the disease. It is a timely need to control the disease transmission before more virulent strains are established in the country. To resolve the epidemiology of Leishmaniasis further studies on the parasitic aspects and entomological studies of vector aspects are most important. Harmonizing with these biological phenomena, continuous surveillance, improving case detection programs at the community level and implementing management protocols and control activities are necessary to eliminate Leishmanisis in Sri Lanka

Keywords: Leishmaniasis, *Leishmania*, Sand fly, Sri Lanka

Leishmaniasis

Leishmaniasis is a vector- borne disease caused by species of the parasitic protozoan *Leishmania* and transmitted to humans through the bite of infected Phlebotomine (Diptera: Psychodidae) female sand flies. It is a mammalian disease and humans can be transmitted from zoonotic reservoir hosts. The disease is widespread throughout the world and is found in 98 countries in Europe, Africa, Asia and America and has become an enormous global burden. It has been listed as one of the eight major neglected tropical parasitic disease (WHO 2017).

In humans, the disease clinically manifests in three main forms; Visceral Leishmaniasis (VL), Cutaneous Leishmaniasis (CL) and Muco-Cutaneous Leishmaniasis (MCL). The most common form, cutaneous leishmaniasis causes Cutaneous lesions on exposed parts of the body, leaving life-long unpigmented scars and serious disability. CL occurs in different forms; Localized Cutaneous Leishmaniasis (LCL), Diffuse Cutaneous Leishmaniasis (DCL) and Muco-Cutaneous Leishmaniasis (MCL). LCL is characterized by skin lesions and ulcers on exposed parts of the body, leaving permanent scars. DCL is less common and is distinguished from LCL by the development of multiple, slowly progressing nodules without ulceration involving the entire body (Aste and Biggio 2002).

Visceral leishmaniasis (Kala-azar) is a most serious chronic systemic disease where the parasite invades visceral organs. If untreated, VL is fatal in over 95% of cases. It is the same *Leishmania donovani* that causes CL and VL in humans in two different localities. In untreated conditions of *Leishmania braziliensis*, a different species able to spread rarely to mucous and sub cutaneous tissues of the nose, mouth and throat causing ulcers. Muco-Cutaneous Leishmaniasis is restricted only to Latin American regions (WHO 2017).

History of Leishmaniasis

Leishmaniasis has a long history, dating back to 2500 B.C., with several primitive descriptions of the disease having been found in ancient writings and recent molecular findings from ancient archeological material (Steverding 2017). With the Spanish colonization of the Americas at the beginning of the 16th century, cocoa growers working in the lower eastern slopes of the Peruvian Andes suffered from the destruction of the nose and lips; named "Andean sickness". In the 18th century an Indian physician wrote the first detailed description of Kala- azar "black fever" now known as Visceral Leishmaniasis (Mohammad *et al.* 2016). In first half of 20th century William Leishman discovered ovoid bodies in the spleen of a British soldier who was experiencing bouts of fever, anaemia, muscular atrophy and swelling of the spleen hence the disease became known as Leishmaniasis. He observed ovoid bodies were degenerated forms of trypanosomes and therefore he proposed that the illness was a form of trypanosomiasis (Steverding 2017). An Irish doctor Charles Donovan concluded that the ovoid bodies were not degenerated trypanosomes but a novel protozoan and that the clinical picture of the cases resembled that of kala-azar, hence ovoid bodies were referred to as *Leishmania donovani*.

Current situation of Leishmaniasis in the world

Leishmaniasis still remains a major health problem throughout the world. According to the World Health Organization (2017) over 90% of new cases occurred in just 13 countries: Afghanistan, Algeria, Bangladesh, Bolivia, Brazil, Columbia, Ethiopia, India, Iran, Peru, South Sudan, Sudan and Syria. It is estimated that between 0.9 and 1.7 million people are newly diagnosed annually. Among them the most common is Cutaneous Leishmaniasis with 0.7–1.3 million new cases and the most severe Visceral Leishmniasis with 0.2-0.4 million new cases occurring. Only a small fraction of them will develop the disease and 20,000–30,000 will eventually die (WHO 2016).

In the Mediterranean basin and South East Asia, the most common form of the disease is Visceral Leishmaniasis while in East Africa and North-Africa-Eurasia, Cutaneous Leishmaniasis is the most common form. In the Americas the epidemiology of cutaneous leishmaniasis is very complex although both of VL and CL forms are present (WHO 2017).

The increase in the number of leishmaniasis cases observed during the last 25 years throughout the world is due to several factors. The disease mainly affects poor people in Africa, Asia and Latin America, and is associated with malnutrition, population displacement, poor housing, weak immune system and lack of resources (Oryan and Akbari 2016). The World Health Organization (2017) has targeted the elimination of the most virulent form, Visceral Leishmaniasis from the Indian sub-continent in three major countries Bangladesh, India and Nepal by year 2020.

Leishmaniasis in Sri Lanka

Sri Lanka is the newest recorded focus of Leishmaniasis and it is caused by most virulent *Leishmania donovani* (Siriwardana *et al.* 2007). In Sri Lanka Leishmaniasis was not recorded until 1990 and it took the nature of an imported disease found among overseas employees returning to the country. However, in 1992 local transmission of this disease was recorded in Ambalantota (Athukorale *et al.* 1992) and a second case was reported in 1995 from Mahiyangana (Siriwardana *et al.* 2012). Until 2001, few sporadic cases were detected locally; it was stated that Cutaneous Leishmaniasis is an emerging epidemic in the island (Athukorale *et al.* 1992; Siriwardana *et al.* 2012). In 2009, leishmaniasis became notifiable. The number of cases reported in 2009 was 674, in 2010 it was 428, and in 2011 there were 930 cases. Polonnaruwa, Hambantota, Matara and Anuradhapura districts were highly endemic: (Sandanayaka *et al.* 2014).

Figure 1. Symptoms of Cutaneous Leishmaniasis. (a) Scar in belly, (b) Scar with central depressed depigmented area surrounded by raised crusty edge, (c) Scar in elbow and (d) Scar in leg. Photos were taken from patients reported at Anuradhapura District.

According to Siriwardana *et al.* (2007), patients with clinical characteristics of Leishmaniasis (Figure 1a, 1b, 1c, and 1d) were reported in 2003 confirming the presence of locally acquired CL in Sri Lanka. Since then Leishmaniasis has become established in Sri Lanka with an explosive increase in number. Now Sri Lanka is endemic for Cutaneous Leishmaniasis which affects outdoor working population in almost all provinces. The age groups of males from 21 to 40 were highly affected by this disease during the initial phase of its outbreak and majority of them were soldiers working in Northern Sri Lanka (Siriwardana *et al.* 2012). The reason for spreading has been associated with the movement of military personnel into former uninhabited areas and population movements due to the civil war. In addition, presence of vectors may increase the prevalence of the disease (Ferro *et al.* 2015). At present, Leishmaniasis is more common among farmers (Siriwardana *et al.* 2012).

Agreeing with Rajapaksa *et al*. (2007), the majority of leishmaniasis cases were recorded in North-Central Provinces and fewer cases were reported in southern parts of the country. The highest number of CL patients was recorded in Anuradhapura, Ratnapura, Matara, Hambanthota, Matale and Polonnaruwa districts during the last few decades (Figure 2). In the Matara district, an extraordinary increase of leishmaniasis cases was recorded during Februar–March and August–September following the monsoon period. Of these cases, the highest population of patient was recorded in rural areas (Rajapaksa *et al*. 2007). Over 2500 cases were recorded throughout the country since 2001 (Karunaweera and Rajapaksha 2009) and this number is seen as an under-representation of the true incidence of the disease. As this is a serious health issue in the country, a national action plan has been implemented to control of this disease (Nawaratna *et al.* 2007).

Parasitic aspects

The disease causing agent of cutaneous leishmaniasis is *Leishmania donovani*. With the spreading of the disease, biochemical studies of the parasite were started in 2001. The results of these studies confirmed that the parasite in the country was *L. donovani* MON 37 (Karunaweera *et al*. 2003). It was also evident that the local species were genetically different from the members of the same species which were described earlier (Siriwardana *et al*. 2007). However, according to Karunaweera and Rajapaksha (2009), there is a very close similarity between the local parasite *Leishmania donovani* MON-37 and the parasite causing visceral leishmaniasis in India *Leishmania donovani* MON-2).

Currently about 40 species of *Leishmania* are described and the disease outcome is different with the species. However, more than 925 sand fly species have been described, only a few species are responsible for the transmission of the disease (Dawit *et al.* 2013). Therefore, there is species specificity between the parasite and the vector. This species specificity is dependent on the molecular factors of the parasite and the vector which cause the parasite to infect, survive and to multiply within the vector's mid gut (Ramalho-Ortigao *et al*. 2010).

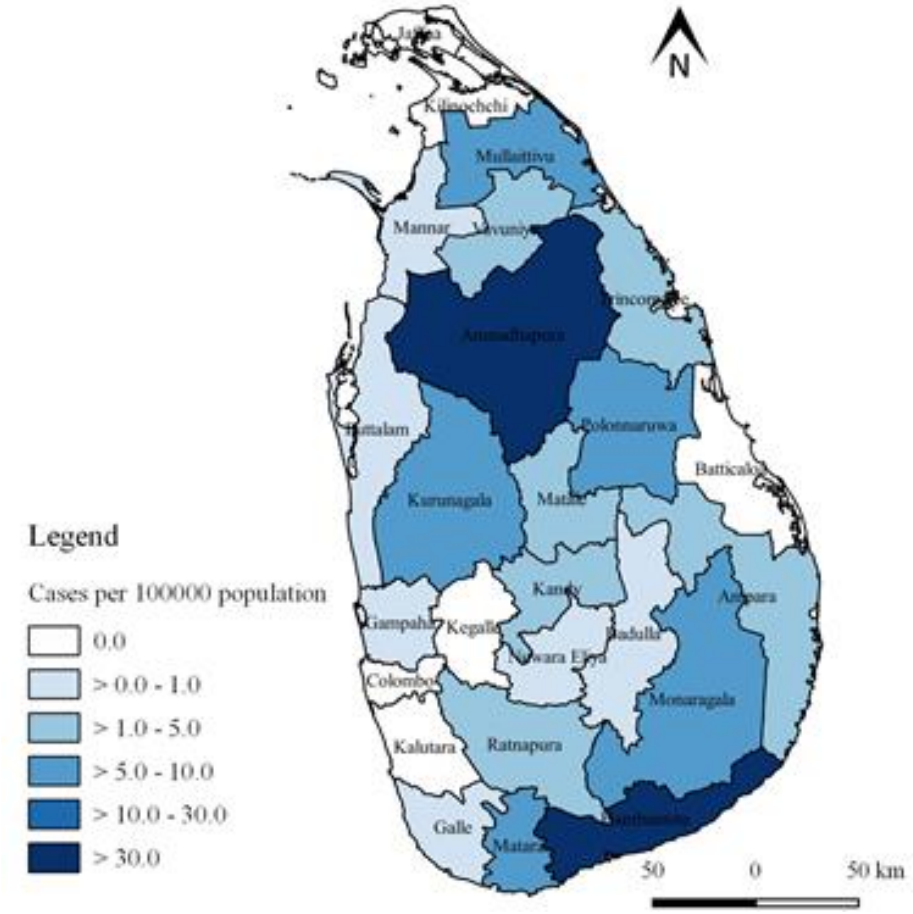

Figure 2. Graphical illustration of lesihmaniasis case distribution of Sri Lanka in 2015 (Source: Epidemiology Unit, Sri Lanka)

Vector aspects

Even though substantial amount of research has been carried out regarding different aspects of the parasite of leishmaniais; *Leishmania*, only handful of research have been reported regarding the vector biology, vector behavior, vector ecology and vector control in Sri Lanka.

Among the described species of san flies, only three genera, *Phlebotomus, Lutzomyia* and *Sergentomyia* are known to feed on vertebrate blood and only about 30 of them have been positively identified as vectors of the disease (Bari and Rahman 2008). Even though sand fly fauna of Sri Lanka has not been adequately studied, a few of studies indicate that most predominant sand fly is *Phlebotomus argentipes* (Ozbel *et al.* 2011). This is the primary vector of *Leishmania donovani*, the etiological agent of Visceral Leishmaniasis in India. Phlebotominae sand flies are found throughout the intertropical and temperate regions of the world.

The adults of sand flies are small bodied insects ranging from 1.5-2.5 mm (Figure 3). They possess hairy appearance on the body and have long thin legs. They keep their long wings at a 45° angle on their back of the body when they are resting or feeding. Both male and female adult sand flies need sugar for energy and survival. However, only the females need regular blood meals from mammals. This blood meal is used to mature their eggs. Alexander and Young (1992) stated that, sand flies can fly about 200 m according to their mark release recapture method. This was a decent observation of dispersal of these vectors. The sand fly bite is believed to occur from dawn to dusk. They don't make noise; rest outdoor in bushy areas.

Figure 3. Phlebotomine sand fly (100x10)

There are certain sand fly species which can harbor several species of *Leishmania* parasites. For example, *Lutzomyia longipalpis* is a sand fly species that can harbor *Leishmania infantum chagasi* or *Leishmania mexicana* (Pitaluga *et al*., 2009). In contrast to these kinds of vectors, other sand fly species are considered as specific as they only can be infected with a specific *Leishmania* species. This kind of relationship was observed between *Phlebotomus papatasi* and *Leishmania major*. *Leishmania* parasites undergo a complex developmental process in the mid gut of vector. However, there is a harmonic interplay between the parasite and sand fly for the survival of the parasite (Pitaluga *et al*., 2009).

Only the infected female sand fly transmits parasites contained in the blood it sucks from human or other mammalian host, in order to obtain the protein necessary to develop its eggs. In the sand fly's mid gut amastigotes of *Leishmania* develop into promastigotes and within one week they convert to infective promastigotes and migrate forward to proboscis (Kamhawi 2006). When the sand fly feeds again, regurgitate the promastigotes into the bite site. There after clinical disease become apparent within two to three weeks after the infection according to the nature of parasite. Wild rodents, marsupials and carnivores including jackals and domestic dogs and other mammals serve as reservoir hosts for *Leishmania* where human serve as an accidental host (*Anjili et al*. 1998, Barnes *et al.* 1993, Beck *et al*. 2008, Brazil *et al.* 1987).

Ecological aspects of the vector

Depending on environmental factors; temperature and precipitation, physical factors; habitat availability and natural barriers, biotic factors; abundance and distribution of hosts dispersal of Phlebotominae sand flies is varying. Even though previous studies revealed that altitude has a high impact on the distribution of sand flies (Belen *et al.* 2006), according to Guernaoui *et al.* (2006) altitude is not an important ecological factor by itself, but it can act on distribution of sand flies by the diversity of habitats.

Risk factors

The main risk factors of spreading the Leishmaniasis are socioeconomic conditions, population mobility, environmental changes and climate change. As the socioeconomic conditions mainly poverty enhance the risk of Leishmaniasis in vector prevalent areas. Poor housing conditions and low sanitary conditions may increase the breeding sites and the resting sites of the sand flies. Population mobility; the migrations of people to the areas where the disease transmitting cycle exist may positively influence to spreading the Leishmaniasis. Urbanization, intrusion of agricultural farms settlements into forest areas and domestication of transmission cycle are the environmental changes that can influence domestic type of Leishmaniasis from its sylvatic type. (Oryan and Akbari 2006).

Climate changes strongly affect with the transmission of Leishmaniasis. Temperature fluctuations, changes of humidity and rain fall highly effect for the distribution and abundance of sand fly population. Small changes of temperature can have a profound effect on the development of protozoa in the sand flies. Drought, flood and famine conditions that resulting from climate changes can lead to enormous displacement and migration of people to areas where the Leishmanias is transmitting (WHO 2016).

Studies on prevalence and risk factors of Leishmaniasis were carried out in different areas; mainly Northern and Southern areas of Sri Lanka in early 2000 (Karunaweera 2003, Perera *et al.* 2004).These studies revealed that majority of young adult males who involved in outdoor activities more time in the North were associated with Leishmaniasis favoring an outdoor transmission (Perera *et al*. 2004) while in Southern Sri Lanka age between 11-40 years, housing conditions and house hold clustering were correlate with increasing risk of acquiring the disease, assisting peri- domestic transmission.

Disease control, constraints and challenges

Unavailability of vaccine and absence of proper treatment methods leads to search for best vector control programs. In order to control the vector, key components are elucidation of the life cycle, biology, ecology and behavior of the vector. Although leishmaniasis and sand flies have been reported from many countries all over the world including Sri Lanka, knowledge of biological, ecological and behavior aspects of the sand fly species are scanty. Major contributory factors face by scientists to study these aspects are difficulties in maintaining and establishing laboratory colonies of sand flies. This is mainly due to its delicate nature, narrow limits of tolerance to environment and difficulties in mating under laboratory conditions (Yaghoobi-Ershadi *et al.* 2007). In addition, sand flies

shed large numbers of hairs which are inhaled by the collector and can cause respiratory problems. Furthermore, their resting sites involve dark and humid microhabitats with potential danger of fungal and bacterial infections, such as histoplasmosis or Q-fever caused by *Coxiella burnetti* (Volf and Volfova 2011).

Vector monitoring, control and notification of the disease, health education are most important initiatives for the prevention of Leishmaniasis in Sri Lanka. Other than that continuous surveillance, improvement of early case detection at the community level and implementing management protocols and control activities will be necessary for effective control of increasing Leishmaniasis patients in the country. To achieve the goal both parasite and vector studies should be further carried out. Therefore, continued research activities on parasite and vector and establishing a disease monitoring system can affect the control of Leishmaniasis in Sri Lanka.

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